REMARKS

Claims 4-9 and 12-16 are pending in this application. Claims 1-3 and 10-11 have been canceled without prejudice or disclaimer herein. Claims 4 and 12-14 have been amended herein.

Applicants note that the Examiner has indicated in the Office action summary that claims 1-14 are pending. However, the specification as filed has **16** claims, and Preliminary Amendment filed on March 13, 2002, amended claims 1 and 5-9, but did not cancel any claim. Although pages 36-39A of the PCT article 34 amendment contain amended versions of claims 1-14, they do **not** represent a cancellation of claims 15 and 16. Therefore, claims 15 and 16 are also pending in this application, and examination of these claims is respectfully requested.

Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,287,769 (Office action point no. 2).

The rejection of claims 1-3, 10 and 11 is moot in view of the cancellation of these claims without prejudice or disclaimer. The rejection of claims 4-9 and 12-14 under obviousness-type double patenting is respectfully traversed, and reconsideration of the rejection is respectfully requested.

Applicants note that claim 1 of Inoue '769 reads:

1. A method of amplifying DNA fragments in a population of DNA molecules obtained from a source, the method comprising:

preparing a plurality of primers selected to have proper amplification probabilities, as assessed using an electrophoretic pattern produced by amplification of DNA obtained from a similar source; and

simultaneously applying a polymerase chain reaction (PCR) method to a plurality of different DNAs with each of said plurality of primers, thereby amplifying fragments of said plurality of

different DNAs.

Claim 1 of Inoue '769 therefore recites a method using a plurality of primers having "proper amplification probabilities", which the Examiner is apparently equating with the "specific amplification probability" of the primer in claim 1 of the present application. Claim 6 of Inoue '769 reads:

> 6. A method of assaying a group of microorganisms obtained from a source, the method comprising:
>
> preparing a plurality of primers selected to have proper amplification probabilities, as assessed using an electrophoretic pattern produced by amplification of DNA obtained from a similar source;
>
> simultaneously applying a PCR method to DNA of a plurality of different microorganisms with each of said plurality of primers, thereby amplifying fragments of said DNA of said microorganisms; and
>
> classifying said amplified fragments by a discrimination method for discriminating a plurality of different microorganisms included in said group of microorganisms.

Applicants note that the claims of Inoue '769 do not recite use on the nucleic acid of an intestinal bacterial group in a bacterial flora sample.

The Examiner states that "the method of instant claims 1-9 is a species that would render obvious to the genus method claims 1-4 and 6-11 of U.S. Patent No. 6,287,769." Applicants respectfully disagree. Obviousness-type double patenting requires that the claimed subject matter of the application is not patentably distinct from the subject matter of the commonly owned patent, and this parallels the guidelines for obviousness rejections under 35 U.S.C. 103(a) (see MPEP 804).

In this case, the Examiner is considering the method of U.S. '769 a "genus" in which all possible applications of this method to all possible (and unspecified) different populations of DNA molecules (which are essentially infinite in number) are the "species". However, a very large or near infinite genus does **not** automatically render each of the species obvious.

What is at issue is whether it would have been obvious, to one of skill in the art at the time of filing of the present application, to modify the claims of Inoue '769 to have the "population of DNA molecules taken from a source" be limited to the nucleic acid of an intestinal bacterial group sample. The Examiner has cited no suggestion or motivation in the general art for this modification of Inoue's claims.

Moreover, Applicants submit that claims 4-9 and 12-14 are directed to the method and the analyzer in which the probes are arranged on specific positions in a detector. This does not represent a "species" of the claims of U.S. Patent No. 6,287,769.

Again, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11-17 of U.S. Patent No. 6,274,306 (Office action point no. 3).

The rejection of claims 1-3 is moot in view of the cancellation of these claims without prejudice or disclaimer. The rejection of claims 4-9 is respectfully traversed, and reconsideration of the rejection is respectfully requested.

Claim 11 of Inoue '306 reads:

11. A method of assaying microorganisms comprising steps of:
introducing a carrier at a site for sampling a group of microorganisms, the carrier being formed by a material body, wherein the body has a plurality of pores and does not comprise DNA;
extracting the group of microorganisms by crushing said carrier, whereby said group of microorganisms is liberated from said carrier;
amplifying DNA obtained from said group of microorganisms by polymerase chain reaction using a plurality of primers having different amplification probabilities, whereby amplified DNA fragments are obtained;
classifying said amplified DNA fragments by a discrimination method; and

discriminating said plurality of different microorganisms included in said group of microorganisms.

Claim 11 of Inoue '306 therefore discloses extracting a group of microorganisms from a body, and amplifying DNA obtained from the group of microorganisms using primers having different amplification probabilities. The Examiner states "Both the instant application and U.S. Patent No. 6,274,306 have coincident scope." By this, the Examiner presumably means that the present claims are subordinate to claims 11-17 of Inoue et al. However, Applicants submit that this is **not** a proper basis for a *prima facie* case of obviousness-type double patenting. As with the rejection over Inoue '769, the question at issue is whether it would have been obvious to modify the "group of microorganisms" in claim 11 of Inoue '306 to be an "intestinal bacterial group". Applicants submit that the Examiner has cited no suggestion or motivation in the general art for such a modification of the claims of Inoue '306, and that there is no obviousness-type double patenting over Inoue '306.

Moreover, Applicants submit that claims 4-9 are directed to the method and the analyzer in which the probes are arranged on specific positions in a detector. This does not represent a "species" of the claims of U.S. Patent No. 6,274,306.

Again, reconsideration and withdrawal of the rejection are respectfully requested.

Claim 4 is objected to because of informalities (Office action point no. 4).

The objection to claim 4 is overcome by the amendment to the claim, correcting the typographical error.

Claim 14 is objected to because of informalities (Office action point no. 5).

The objection is overcome by the amendment to claim 14, clarifying the wording of the claim.

Claims 10-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite (Office action point no. 6).

a. The Examiner states that claims 12-14 are indefinite because of the phrase "derived from". This rejection is overcome by the amendments to claims 12 and 13, in which the wording is amended: "~~formed by nucleic acid derived from the~~ having a nucleic acid sequence occurring in the genome of the intestinal bacterial group". This wording incorporates the meaning of "derived from" as commonly understood in the art, and is supported by the general disclosure of the specification, for example on page 11, lines 17-25, and page 29, lines 5-11.

b. The Examiner rejects claim 10 because of the phrase "an electrophoretic pattern fractionated in said electrophoretic unit." The rejection is moot in view of the cancellation of claim 10 without prejudice or disclaimer.

c. The Examiner rejects claims 11-14 because of the phrase "hybridizes said amplified nucleic acid and a specific probe." The rejection of claim 11 is moot in view of the cancellation of claim 11 without prejudice or disclaimer. The rejection of pending claims 12-14 is respectfully traversed. Applicants submit that this claim can be understood by one of skill in the art. The phrase "hybridizes said amplified nucleic acid and a specific probe" means that different probes are

arranged on a plurality of positions for hybridizing amplified nucleic acid with these probes.

Claims 1-2 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Hamad et al. (*J. Applied Microbiology*, 1997, Vol. 83, 764-770) (Office action point no. 8).

The rejection of claims 1 and 2 is moot in view of the cancellation of claims 1 and 2 without prejudice or disclaimer. The rejection of claim 9 is respectfully traversed.

Hamad et al. disclose a study of the microflora of a Sudanese sorghum flour. Bacteria were grown from sorghum sourdough (page 765, column 1) and DNA isolated, and *in vitro* amplification of 16S rRNA was conducted, followed by partial sequencing using the ThermSequenase kit. In addition, RAPD-PCR was performed using the universal primer M13V.

In the rejection, the Examiner states that the arbitrary primer of Hamad et al. for RAPD-PCR meets the limitations of the specific PCR primer of the claim.

However, Applicants note that present claim 9 requires "amplifying nucleic acid of an intestinal bacterial group in a sample extracted from a subject ..." This clearly implies a sample extracted from an animal having an intestine. Hamad et al. does not appear to disclose or suggest tests on any such sample; Hamad's samples are from fermented sorghum and this does not constitute an intestinal bacterial group as recited. The fact that some of these bacteria may be capable of growing in the intestine is irrelevant.

Moreover, in the RAPD-PCR carried out in the report by Hamad et al. (Journal of Applied Microbiology, 1997, Vol. Pg. 746-770), the primer is employed from amplifying only an isolated bacterium. In contrast, the primer having a specific amplification probability is employed for amplifying both of an isolated bacterium and a bacterial flora (state where a plurality of bacteria are

mixed with each other) in the present invention. Employment of the primer having a specific amplification probability is advantageous in the point that a single type of DNA fragment can be amplified from a single type of bacterium on the average and the point that the DNA fragment of each bacterium can be readily found out from a plurality of DNA fragments obtained by measuring the bacterial flora. Thus, the present invention is different from the teaching by Hamad et al.

In addition, claim 9 recites in a combination of PCR amplification and DNA-DNA hybridization arranging probes on specific positions in a detector.

Applicants therefore submit that claim 9 is not anticipated by Hamad et al.

Claims 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilding et al. (U.S. Patent No. 5,498,392) (Office action point no. 9).

The rejection of claims 10 and 11 is moot in view of the cancellation of these claims without prejudice or disclaimer.

Claims 3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamad et al. (*J. Applied Microbiology*, 1997, Vol. 83, 764-770) in view of Mullis et al. (U.S. Patent No. 4,800,159) (Office action point no. 11).

The rejection of claim 3 is moot in view of the cancellation of claim 3 without prejudice or disclaimer. The rejection of claim 6 is respectfully traversed.

Mullis et al. discloses a process for amplifying, detecting and/or cloning nucleic acid sequences. The process comprises treating separate complementary strands of the nucleic acid with a molar excess of two oligonucleotide primers, extending the primers to form complementary

extension products, and detecting the sequence amplified.

The Examiner cites Mullis et al. for disclosing a method of polymerase chain reaction in which the amplification products are detected by labeled probe. The Examiner states that "The teachings of Mullis et al. suggest that the intestinal bacterial flora would have been amplified and detected by hybridizing a nucleic acid probe."

Although Mullis et al. does disclose that bacteria can be analyzed (column 19, line 11), the reference does **not** appear to disclose analyzing nucleic acid from an intestinal bacterial group from a subject, as required by claim 6. No combination of Hamad et al. and Mullis et al. can provide this limitation of the present claims.

More significantly, the present invention requires that DNA fragments of a **plurality of bacteria** are simultaneously amplified and detected by probes arranged on **specific positions**.

According to the description of Mullis et al. (United States Patent No. 4,800,159), only the sequence of a desired **single type of DNA fragment** is amplified in synthesized nucleic acid sequence. In contrast, a plurality of types of DNA fragments can be amplified by a specific PCR primer and the original bacteria for the respective DNA fragments can be investigated by DNA-DNA hybridization according to the inventive method.

There is also no disclosure or suggestion in either reference of the limitation of probes arranged at specific positions on a detector.

Applicants therefore submit that claim 6 is novel and non-obvious over Hamad et al. and Mullis et al., taken separately or in combination.

Claims 4-5, 7-8 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamad et al. (*J. Applied Microbiology*, 1997, Vol. 83, 764-770) in view of Wilding et al. (U.S. Patent No. 5,498,392) (Office action point no. 12).

The rejection of claims 10 and 11 is moot in view of the cancellation of these claims without prejudice or disclaimer. The rejection of claims 4-5, 7-8 and 12-14 is respectfully traversed.

The Examiner states that "One of ordinary skill in the art would have been motivated to apply the device of Wilding et al. to the method of Hamad et al. for studying characterization of the bacterial flora." However, Applicants have noted above that Hamad et al. does not teach or suggest any study on nucleic acid of an intestinal bacterial group in a sample extracted from a subject. Wilding also does not teach or suggest this, and therefore, method claims 4-5 and 7-8 are novel and non-obvious over this combination of references.

Applicants further note there is no teaching or suggestion in the descriptions of Wilding et al. (United States Patent No. 5,498,392) and Hamad et al. to estimate rapid simultaneous detection of a **plurality of bacteria**. Either method is employed for amplifying a single DNA fragment, and hybridization is merely applicable to detection of a single DNA fragment or the original organism (bacterium or the like) therefore.

According to the present invention, it is possible to simultaneously amplify DNA fragments corresponding to a plurality of bacteria respectively and simultaneously detect the plurality of obtained DNA fragments with a plurality of specific probes whose positions are fixed. The types of pathogenic bacteria can be investigated without prediction by an analyzer based on this method. In other words, the type of a pathogenic bacterium (even a plurality of pathogenic bacteria) can be investigated from the positions of hybridized probes. It is also possible to simultaneously investigate

what kinds of bacteria inhabit the intestines.

Moreover, claims 12-14 recite a probe formed from nucleic acid derived from the intestinal bacterial group. This is not taught or suggested in either reference, and therefore apparatus claims 12-14 are further non-obvious over the references.

Applicants therefore assert that pending claims 4-5, 7-8 and 12-14 are novel and non-obvious over Hamad et al. and Wilding et al., taken separately or in combination.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact Applicant's undersigned agent at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, Applicant respectfully petitions for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully submitted,

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